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Dr. Larry G. Hart
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Dear Dr. Hart:

Pursuant to the notice in the Federal Register: December 14, 1998 (Volume 63, Number 229), I am submitting comments regarding the nomination to list alcoholic beverages in the Natonal Toxicology Program's (NTP) 9th Edition of the Report on Human Carcinogens. Also attached, as part of my response, are copies of my comments to Dr. Jameson prior to the NTP Board of Scientific Counselors meeting on December 2-3 at NIEHS and also my comments made at that meeting. Please consider these as my formal response for the record to the action taken at that meeting.

Sincerely,

William J. Waddell, M.D.
Professor and Chair, Emeritus

Enclosures

Response to the NTP Proposed Classification of Alcoholic Beverages as a Known Human Carcinogen

by
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These comments are a summary of previous statements made by me concerning the proposed carcinogenicity listing of alcoholic beverages and include, in addition, my reaction to the discussion by the NTP Board of Scientific Counselors Report on Carcinogens Subcommittee meeting on December 2-3. At that meeting, I presented a brief summary of my analysis of the literature on alcohol and cancer, and, written comments were submitted before and during the meeting for review by the Subcommittee. Copies of those previously submitted comments are attached. I have been asked by the beverage alcohol industry to provide these further comments which are entirely my own personal views about the potential listing by the NTP of alcoholic beverage consumption.

By way of introduction, a brief outline of my background can be found in the attached letter to Dr. Jameson that was submitted prior to the NTP meeting. Further details can be found in my curriculum vitae, which is attached. Importantly, I have conducted research on alcohol and chemical carcinogenesis since 1977 and attended the meeting at IARC in 1987 on "Alcohol Drinking" when the decision was made to assign a carcinogenic designation.

As an executive summary or overview, my observations are that the NTP's evaluation of alcoholic beverages as a carcinogen is based entirely on epidemiological studies and that those studies are either so seriously confounded or are so weak and inconsistent that there is no justification to label alcohol as a carcinogen. The sites of the body where alcohol beverage consumption is alleged to be carcinogenic by the NTP are the upper aerodigestive tract (oral cavity, pharynx, larynx, and esophagus), liver, and breast. The epidemiological studies on the aerodigestive tract are almost all

confounded by concurrent tobacco smoking. In the few reports that examine nonsmoking drinkers, there is no increase in cancer in the upper aerodigestive tract at moderate levels of drinking; although some studies do find an increase in cancer at levels in the range of that consumed by an alcoholic, oral hygiene, diet, and other lifestyle factors could well be confounders. The liver studies are confounded by hepatitis B and C viruses and the breast studies are inconsistent, some studies showing a weak association, some showing no association and some showing a negative association. In the final analysis, evidence cannot support any conclusion that beverage alcohol consumption is a carcinogen.

There have been more than forty studies on the possible carcinogenicity of alcohol in experimental animals. Not a single valid experimental study has indicated that alcohol is a carcinogen. Every individual, review, or agency that has examined the experimental data has concluded that alcohol is not carcinogenic to experimental animals. Consequently, any association and any inferences from such an association, must be made only from epidemiological studies.

Confounding is always a possibility in human studies and certainly must be examined carefully when the many animal studies have all failed to show that alcohol causes cancer in any tissue. Possible confounders are best examined by the particular site of the tumor. The sites where the incidence of cancer is elevated in epidemiological studies are the upper aerodigestive tract (oral cavity, pharynx, larynx, esophagus), liver and possibly breast.

Since the vast majority of drinkers in the populations studied have also been smokers and the tissues that receive the largest initial dose of both smoke and alcohol are the oral cavity, pharynx, (epi)larynx, and esophagus, confounding by tobacco smoke is an obvious issue. There are also human studies to support the hypothesis that the role of alcohol is principally important only in conjunction with tobacco use (Jaber, 1998). Furthermore, poor oral hygiene (Graham et al, 1977) and diet (Gridley, et al, 1990) have also been shown independently to be associated with cancers of these upper aerodigestive tract sites. The NTP Background Document correctly acknowledges the problem of confounding by tobacco smoking in cohort studies and consequently cites the largest case-control studies and the Longnecker and Tseng review as evidence for the association.

Very few of the reports in the literature contain information on nonsmoking drinkers. Most of the studies have been "adjusted" for smoking to estimate the effect from alcohol. It is most important to understand that statistical "adjustment" is not the same as correction or control. Although there are several methods for statistical multivariate analysis, when both alcohol consumption and tobacco smoking coexist in these studies, there is no way to separate out the possible unique biological contribution of alcohol.

Since "adjustment" for smoking is problematic at best (and from our understanding of ethanol it is probably deceptive) one needs to examine the reports that contain information on true nonsmoking drinkers. I examined all of the reports that contain data on the upper digestive tract in nonsmoking drinkers for the presentation to the Subcommittee on December 2, 1998; in addition, other papers known to be in the literature were included in that report. (From the ensuing discussion by the Subcommittee, it is apparent that it was not understood that my summary, restricted to only five minutes, addressed all reports containing nonsmoking drinkers.) Details of those results can be found in a copy of those comments I submitted which are attached. It should be emphasized that those comments included *all* reports that had data (or were cited as having data) on nonsmoking drinkers for the oral cavity, pharynx, larynx, and esophagus. In summary, none of the papers report an increase in cancer in the upper aerodigestive tract in nonsmoking drinkers at moderate levels of drinking; several report an actual *decrease* in the incidence of cancer among these drinkers. A few of the papers do find an increase in cancer at higher levels (in the range of that consumed by an alcoholic) where oral hygiene, diet and other lifestyle factors could well be confounders. Dr. Michele Medinsky, a member of the NTP Board of Scientific Counselors Report on Carcinogens Subcommittee, made the same observation in her comments during the discussion on December 2; she referred to this as the alcoholic lifestyle. Clearly, additional confounders arise at levels of alcoholic abuse.

This analysis is in disagreement with the conclusion reached in the Background Document and in the Longnecker and Tseng review. There are two explanations for this disagreement. The first is that those two documents used studies that were statistically "adjusted" for smoking. As previously stated, statistical adjustments are problematic at best. The

second explanation for the disagreement is that the Longnecker and Tseng review flatly misinforms the reader and cites one paper in contradiction to the conclusion of the authors. Ng et al (1993) found no association of cancer of the oral cavity with wine and liquor consumption in nonsmokers and concluded that the association of beer with this cancer may be due to contaminants of beer and *not* alcohol. It is unfortunate that this error has appeared in several Longnecker reviews, continues in the Background Document, and is accepted by the Subcommittee as evidence that alcohol causes cancer in these sites in nonsmokers.

Cancer of the liver is well known to be an effect from infection with hepatitis viruses B and C. None of the studies on alcohol consumption and cancer of the liver has been adequately controlled for infection from hepatitis viruses B and C. Without control of this important confounder, no conclusion of an association between alcohol consumption and cancer of the liver can be made.

Cancer of the breast has been of great interest to both laymen and professionals. There have been dozens of epidemiological studies and numerous reviews. Many potential confounders have been identified including fat intake, smoking, menopausal status, maternal history of breast cancer, education, etc. To my knowledge, none of the studies has controlled for all possible confounders, although many have made statistical "adjustments" for some confounders. In summary, some of the studies show a slight increase, some show a relative risk of unity and some show a statistical decrease in breast cancer with alcohol drinking. None of the studies shows a strong association. These clearly do not satisfy the Hill criteria; certainly no causal inference can be made.

A good example of this controversy can be found in two recent reports. The Smith-Warner et al (1998) pooled analysis of six cohort studies found an increased incidence of breast cancer in only one of six consumption categories (*not* the highest consumption category) and proceeded to predict statistically a 1.41 increased risk ratio with alcohol consumption. In contrast, the very recent Zhang, et al. (1999) analysis of the Framingham Study found no increase in the risk ratio for breast cancer in light to moderate drinkers.

The decision by NTP whether to list alcohol consumption as a known human carcinogen is an important issue for public policy. It is even more important since there is evidence that there is a protective effect from alcohol drinking for cardiovascular diseases. Not only are there good epidemiological studies to support this, but confirming animal and biological mechanistic studies have been done (Zakhari, 1997). There is no doubt that there are health and social risks from alcohol abuse, but that should not be used to influence what should be a careful, informed decision on the potential cancer risks from alcohol consumption, particularly in the absence of smoking. Many people now enjoy alcohol in moderation and do not smoke. Official endorsement of incorrect information eventually erodes confidence in the endorsing agency. NTP should not confuse or mislead the public with a listing about a widely used substance when the information is not conclusive.

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Graham, S, Dayal, H, Rohrer, T, et al (1977) Dentition, diet, tobacco, and alcohol in the epidemiology of oral cancer. JNCI 59:1611-1618.

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Zakhari, S (1997) Alcohol and the cardiovascular system: Molecular mechanisms for the beneficial and harmful action. Alcohol Health and Research World 21(1):21-29.

Zhang, Y, Kreger, BE, Dorgan, JF, et al (1999) Alcohol consumption and risk of breast cancer: the Framingham study revisited. Amer. J. Epidemiology 149:93-105.

Comments of
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Regarding Listing by NTP of Alcoholic Beverages as Carcinogens

My comments will address only the association between alcohol drinking and cancer of the oral cavity, pharynx, larynx, and esophagus. Dr. Rubin will address the association between alcohol drinking and cancer of the breast and liver. It appears, also, that the designation by the NTP of alcoholic beverages as a known carcinogen is based almost entirely on the NTP's assessment of epidemiological associations at these six sites.

As in many recent publications, the Draft RoC Background Document for Alcoholic Beverage Consumption starts by referring to the 1988 IARC Monograph on Alcohol Drinking as unassailable proof that alcohol drinking causes cancer of the oral cavity, pharynx, larynx, esophagus and liver. I was an official observer for the preparation of that Monograph and noted that the final opinion was not unanimous among the members of the working group.

Some of the salient data for the dissent among the members of the working group were published in a letter to the editor (British Journal of Cancer 66, 1200-1201, 1992) by several colleagues and me. A copy of that letter to the editor has already been supplied to the NTP. It was never rebutted satisfactorily by the staff at IARC.

In summary, firstly, at the time of the preparation of that Monograph, there were no adequate studies demonstrating cancer in experimental animals from administration of alcohol. Consequently, the evaluation was based solely on epidemiological studies. Secondly, virtually all the epidemiological studies were confounded by cigarette smoking. And lastly, those few studies not obviously confounded failed to show an increase or in some cases actually showed a decrease in the incidence of cancer. These three observations continue to be problems with all the publications that have appeared since that Monograph.

The NTP Background Document acknowledges the continued lack of supportive animal studies and also acknowledges the problem of confounding by tobacco smoking in cohort studies; consequently, the Document cites the largest case-control studies and the Longnecker and Tseng review as evidence for the classification.

SLIDE 1

This slide quotes Longnecker's review, which appears to be the position of the Document, "the effect of alcohol among lifelong nonsmokers has been clearly demonstrated"; however, the three references do not support that statement. The paper by Ng et al. actually contradicts the Longnecker statement. Not only were the nonsmokers not lifelong nonsmokers, but Ng and colleagues found no association with wine and liquor and concluded that the association may

have little to do with alcohol and that contaminants of beer may be important etiologic factors. The use of this reference by Longnecker is simply misinformation.

SLIDE 2

The other two references (Blot et al. and Baron et al.) have serious flaws to prevent the conclusion of a "clearly demonstrated" effect of alcohol among lifelong nonsmokers. There was either no effect, or it was unknown, in drinkers of less than four or five drinks per day. Above this level of consumption other risk factors, such as oral hygiene and diet may be significant.

SLIDE 3

The risk estimates in the case-control studies on cancer of the oral cavity and pharynx are stated to all have been adjusted for smoking. Adjustment is problematic at best; it does not always fit the shape of the actual dose-response curve and can obscure a zero or even negative effect in nonsmokers. However, some of the case-control studies cited in the Document do contain the raw data on nonsmoking drinkers. Those data contradict the findings from adjustments. This slide shows that several reports found either no increase or an actual decrease, particularly at lower levels of consumption.

In France and Italy there are so few nondrinkers that the effect at lower levels of consumption cannot be ascertained. Control ("nondrinker") groups in studies in France and Italy were those consuming 40 grams of pure alcohol (Brugere et al., 1986) or 5 drinks (Franceschi et al ,1990) per day because there were so few actual nondrinkers. This, of course, will not only obscure a "J" shaped curve (protective at low doses), but if a "J" shaped curve exists, this combining of groups at low doses will make any effect at higher doses appear greater.

SLIDE 4

This slide shows the same analysis for laryngeal cancer. Even with adjustment some reports fail to show a dose-response. The Wynder papers certainly do not support an effect in nonsmokers.

SLIDE 5

This slide shows the same analysis for esophageal cancer. Even with adjustment, two studies fail to show an increase below levels of consumption which may be those of an alcoholic. At these levels other risk factors such as diet, oral hygiene, etc. confound the results. The paper by Tuyns in 1983 is not included in the Document, but it contains raw data on one of the largest groups of nonsmokers with esophageal cancer. The data are presented also for drinkers at lower levels of consumption; this is unusual in France. There is a "J" shaped curve for both males and females which Tuyns did not recognize because he combined drinkers under 40 grams per day as "nondrinkers". If one instead combines the data for males and females to increase the group sizes, the same "J" shaped curve remains with greater confidence. Furthermore, Tuyns' use of the 0-40 gram/day group (who had odds ratios less than unity) as the reference group makes the

odds ratios for other levels of alcohol consumption higher than they would be if the true nondrinkers had been the reference group. This "J" shape curve has been reported by others for alcohol and cancer.

SLIDE 6

This is a graph of the Tuyns data in nonsmoking men and women for levels of consumption up to 120 gms/day; the group consuming more than 120 gms/day had an even higher odds ratio and is not shown. Is one to say that alcohol is an anticarcinogen below 60 grams of alcohol per day? One might also take the position that above 100 grams it may be carcinogenic or that other risk factors become important. In any event, in my opinion, it is a simplistic, unscientific interpretation of the data to merely label the substance as "known carcinogen". Many, if not most people, for personal reasons, will be much more interested in the consumption level below 60 grams per day.

SLIDE 7

Finally, a comment on the mechanisms of carcinogenesis proposed in the document. Acetaldehyde was listed by IARC as an animal carcinogen solely from studies when it was administered by chronic inhalation at doses that caused necrosis of the respiratory epithelium. There were no tumors at any site distant from the respiratory epithelium. No other route of administration produced cancer at any site. These facts do not support the notion that acetaldehyde production may explain the proposed carcinogenicity of alcohol.

The induction of P4502E1 by ethanol and the consequent activation of nitrosamines to reactive intermediates is frequently cited as a possible mechanism of the co-carcinogenic action of alcohol. P4502E1 is an enzyme that metabolizes many small molecules. It is also induced and inhibited by a wide variety of compounds in food and during some physiologic states. This is a complicated interaction and it very well may have some application when considering the interaction with tobacco smoke, but it is totally inconsistent with the data simply to label "alcoholic beverages" independently as a "known carcinogen".

SLIDE 1

"--the effect of alcohol among lifelong nonsmokers has been clearly demonstrated (Baron et al., 1993; Blot et al., 1988; Ng et al., 1993)" **Longnecker and Tseng, in press; (Essentially same statement in Longnecker , 1995)**

-"had never used tobacco products on a daily basis for a period of at least 1 year" -----"The association of beer **(but not wine or liquor)** *and cancer of the oral cavity may have little to do with the alcohol content of beer. Contaminants ---- may be important etiologic factors."*
Ng et al., 1993

SLIDE 2

Blot et al., 1988: No dose response or significant increase in odds ratios with less than 30 drinks per week in nonsmokers (less than 100 cigarettes or cigars or pipes for no more than 6 months)

Baron et al., 1993: No nondrinker group (Italy); Control group <35 drinks per week; "heavy" (35-59 drinks per week) and "very heavy" (60 or more drinks per week) drinker but nonsmoker cases few (1-4) in each of 6 categories (confidence interval not calculated)

SLIDE 3

Case-control, oral-pharyngeal, with raw data on nonsmokers (others contain only adjusted data)

Bross and Coombs, 1976: No significant increase

Martinez, 1969: *Decrease* below 5 drinks per day

Elwood et al., 1984: *Decrease* below 17 drinks/week

Brugere et al., 1986: Nondrinkers: 40 gm/day (France)

Franceschi et al., 1990: Nondrinkers: 5 drinks/day (Italy)

Others not cited:

Day et al., 1993: No sig. increase below 30 drinks/week

Kabat et al., 1994: No sig. increase below 7 oz/day

Nam et al., 1992: *Decrease* below 24 drinks/week

SLIDE 4

Case-control, laryngeal, studies with raw data on nonsmokers (others contain only adjusted data)

Dosemeci et al., 1997: (Adjusted, but no dose response)

Wynder et al., 1956: Only *one* nonsmoker who drank

Wynder et al.,1976: *No* nonsmokers in drinker series

Elwood et al., 1984: (Extrinsic larynx combined with oral-pharyngeal; comments under oral-pharyngeal)

SLIDE 5

Case-control, esophageal, with raw data on nonsmokers (others contain only adjusted data)

De Stefani et al., 1990: (Adjusted, but no increase below 10 drinks/day)

Cheng et al., 1992: (Adjusted, but no sig. increase below 12 drinks/day)

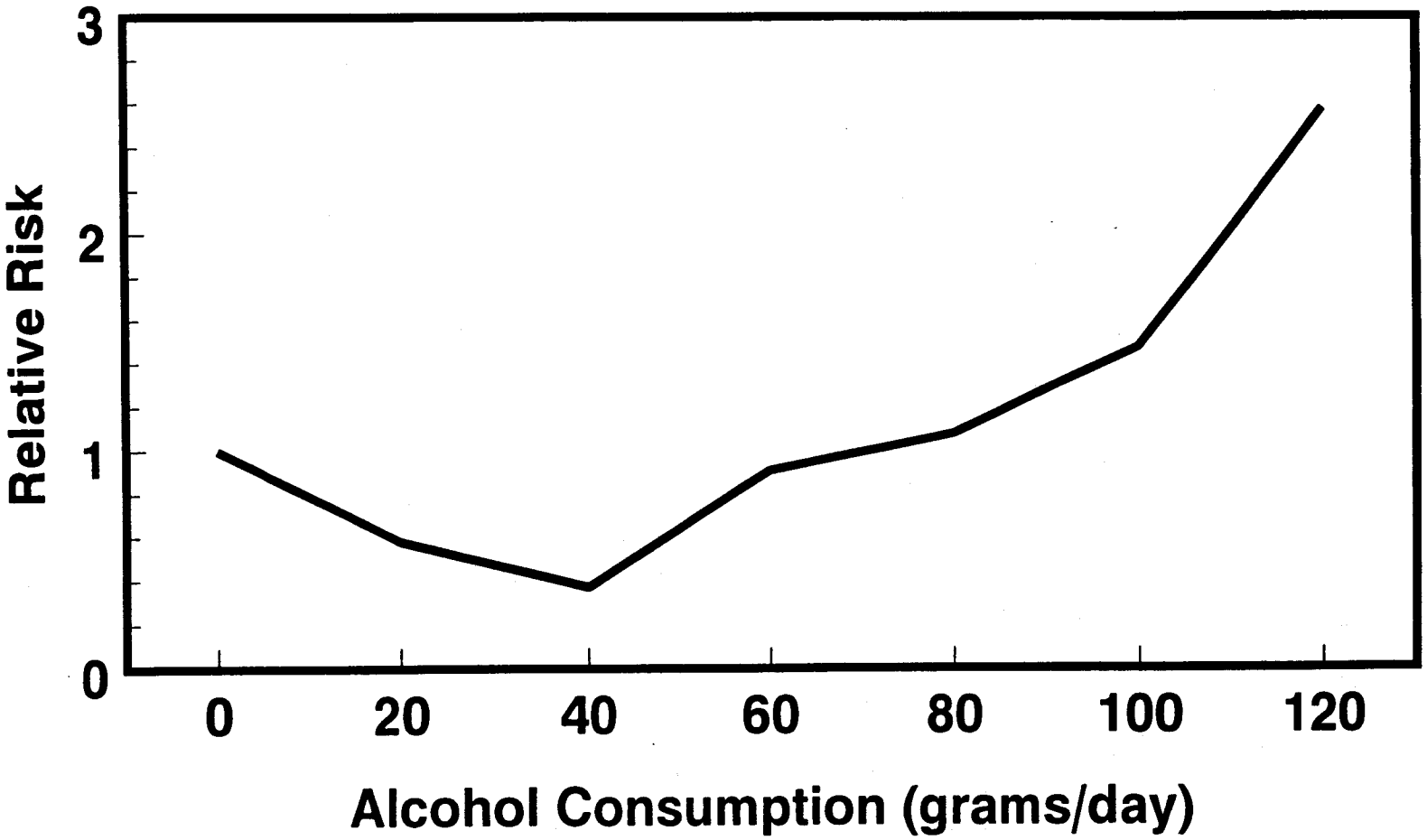
Gao et al.,1994: No sig. increase at any level of drinking

Others not cited:

Tuyns, 1983: Decrease below 60 gms/day "J" curve

SLIDE 6

Relative Risks of Esophageal Cancer Non-Smoking Drinkers (Tuyns 1983 data)



SLIDE 7

Mechanisms of Carcinogenesis Proposed in Document

1. **Acetaldehyde: Is only carcinogenic to animals by inhalation and at doses that cause necrosis of respiratory epithelium.**
2. **Induction of P4502E1 to increase production of proximal carcinogen from nitrosamines: Ethanol also *inhibits* P4502E1 (depending on dose and timing); fasting, obesity, unsaturated lipids, many common foods, thiamine deficiency also affect P4502E1 by induction and/or inhibition**